Subthalamic Nucleus Stimulation Reduces Abnormal Motor Cortical Overactivity in Parkinson Disease

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Background: Based on the basal ganglia model, it has been hypothesized that the efficacy of high-frequency stimulation of the subthalamic nucleus (STN) against parkinsonian symptoms relies on the activation of cortical premotor regions. In previous positron emission tomography activation studies, STN high-frequency stimulation was associated with selective activation of midline premotor areas during hand movements but mainly reduced the regional cerebral blood flow in movement-related areas, particularly at rest.

Objective: To investigate with positron emission tomography the role of regional cerebral blood flow reduction in the clinical improvement provided by STN high-frequency stimulation.

Methods: Seven patients with advanced Parkinson disease, who were markedly improved by bilateral STN high-frequency stimulation, underwent positron emission tomography with $H_2^{15}$O while the right STN electrode was turned off. The patients were studied at rest and during right-hand movements in 3 electrode conditions: no stimulation, inefficient low-frequency stimulation, and efficient high-frequency stimulation.

Results: The main effect of high-frequency stimulation was to reduce regional cerebral blood flow in the left primary sensorimotor cortex, the lateral premotor cortex, the right cerebellum, and the midline premotor areas. The selective activation of the anterior cingulate cortex and the left primary sensorimotor cortex during hand movement under STN high-frequency stimulation was attributed to decreased regional cerebral blood flow at rest, rather than increased activation induced by STN high-frequency stimulation. Akinesia was correlated with the abnormal overactivity in the contralateral primary sensorimotor cortex and the ipsilateral cerebellum.

Conclusion: High-frequency stimulation of the STN acts through the reduction of abnormal resting overactivity in the motor system, allowing selective cortical activation during movement.

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Bilateral high-frequency stimulation of the subthalamic nucleus (STN) markedly improves motor symptoms of patients with advanced forms of Parkinson disease (PD). However, the efficacy of high-frequency stimulation relies on unclear mechanisms. Based on the model of the basal ganglia circuitry, STN high-frequency stimulation would have an effect similar to that of a focal lesion, inactivating the STN and reducing the excessive drive of the STN to the globus pallidus pars interna and to the substantia nigra pars reticulata. This would decrease the inhibitory influence of these latter structures on the activity of the motor relay nuclei, resulting in activation of premotor and motor cortical areas, which are assumed to be underactivated in parkinsonian patients. Therefore, STN high-frequency stimulation is assumed to induce a reactivation of motor cortical areas in PD patients.

This hypothesis can be tested using regional cerebral blood flow (rCBF) measurements in a positron emission tomography (PET) motor activation study. Previously, unilateral STN high-frequency stimulation induced activation of the midline premotor cortical areas during hand movement, but unexpectedly, the main effect of STN high-frequency stimulation was a marked decrease, which was maximal at rest, of rCBF in the primary sensorimotor cortex and in premotor cortical areas. This rCBF reduction was attributed to a decrease of somatosensory feedback associated with the
improvement of rigidity.\textsuperscript{5,6} Alternatively, the rCBF reduction in the motor cortical areas might be beneficial if it corresponds to the decrease of an abnormal overactivity. Indeed, studies with transcranial magnetic stimulation or functional magnetic resonance imaging have evidenced an abnormal overactivity in the motor cortical areas of PD patients who are not taking medication.\textsuperscript{8,9} This overactivity, also found in primate models of PD,\textsuperscript{10} might correspond to an abnormal oscillatory activity in the basal ganglia and motor cortex, contributing to the symptoms of PD.\textsuperscript{11,12} Patients treated with STN high-frequency stimulation exhibit a significant increase of intracortical inhibition.\textsuperscript{13-15} We hypothesized that the reduction of motor cortical activity might explain the motor improvement provided by STN high-frequency stimulation. We performed a PET activation study in PD patients improved by STN high-frequency stimulation, and we specifically investigated the relationship between cortical rCBF and motor performance. We hypothesized that (1) the reduction of rCBF in the motor cortical areas is the main effect of STN high-frequency stimulation and (2) this reduction is associated with the improvement of akinesia induced by STN high-frequency stimulation.

**METHODS**

**PATIENTS**

We selected 7 patients with severe levodopa-responsive PD (mean ± SD age, 54.1 ± 6.2 years) (Table 1). For 10 to 19 years, the patients had an asymmetric, predominantly akinetico-rigid disease and experienced severe motor fluctuations and dyskinesias before surgery. Bilateral stereotactic implantation of quadripolar stimulation electrodes (Model 3387; Medtronic, Minneapolis, Minn) in the STN was performed using a procedure described previously.\textsuperscript{16} Briefly, the targeting of STN and control of electrode location were determined using stereotactic magnetic resonance imaging. During surgery, neurophysiological recordings and clinical assessments were obtained.\textsuperscript{16} All patients were markedly improved by STN stimulation (Figure 1). They gave their written informed consent for this study, which was approved by the local ethical committee.

**CLINICAL EVALUATION**

Patients were studied 10 to 36 months after surgery, the stimulation parameters being stable for at least 4 months. The day before the PET study, each patient underwent a standardized assessment using the Unified Parkinson’s Disease Rating Scale. Antiparkinsonian medications were withdrawn for 12 hours, the right STN electrode was stopped, and the effect of the left STN stimulation was assessed in 3 different conditions: (1) the high-frequency–stimulation condition was identical to the one used to treat the patient (same voltage, same pulse width, and 130- or 185-Hz frequency); (2) the no-stimulation condition, with the electrode switched off, and (3) the low-frequency stimulation (10 Hz). The low-frequency stimulation is a condition with STN switched on without improvement of PD symptoms.\textsuperscript{5} The same motor score was also measured with both stimulators turned on in patients receiving medication. The clinical effects provided by these different conditions were assessed on the right hemibody, using the Unified Parkinson’s Disease Rating Scale III score. Items corresponding to right akinesia, tremor, and rigidity were combined, giving a maximal possible value of 36.

**PET ACTIVATION STUDY**

**Conditions**

After 12 hours of withdrawal from antiparkinsonian drug treatment, the right STN electrode was stopped from 1 hour before the PET study to the end of the examination. We performed a $2 \times 3$ factorial design with 3 stimulation conditions and 2 motor conditions. The stimulation conditions were no stimulation, low-frequency stimulation, and high-frequency stimulation. Each condition was applied as soon as the previous image acquisition was finished and maintained 10 minutes before the following acquisition. The 2 motor conditions were rest and a right-hand movement, consisting of opening and clenching the fist, paced by an auditory stimulus at a 0.5-Hz frequency. The ability of each patient to execute this movement was verified before the PET study. The movement started 40 seconds before the image acquisition. Rest and movement were studied for each different electrode condition, and each acquisition was replicated, giving a total of 12 scans per patient. The order of the conditions was fully counterbalanced across subjects. Only the investigator who modified the STN stimulation parameters was aware of the stimulation conditions. The clinical effect of these stimulations was analyzed posteriori using the videotapes recorded during these sessions. The perfor-

Table 1. Characteristics of Patients and Subthalamic Nucleus Stimulation

<table>
<thead>
<tr>
<th>Patient/ Sex/Age, y</th>
<th>Disease Duration, y</th>
<th>Time Since Implantation, mo</th>
<th>Stimulation: Electrode*/ Frequency, Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/51</td>
<td>12</td>
<td>21</td>
<td>2/130</td>
</tr>
<tr>
<td>2/M/66</td>
<td>11</td>
<td>21</td>
<td>3/130</td>
</tr>
<tr>
<td>3/M/46</td>
<td>10</td>
<td>27</td>
<td>2/185</td>
</tr>
<tr>
<td>4/F/56</td>
<td>15</td>
<td>11</td>
<td>2/185</td>
</tr>
<tr>
<td>5/M/55</td>
<td>13</td>
<td>15</td>
<td>3/130</td>
</tr>
<tr>
<td>6/F/51</td>
<td>18</td>
<td>36</td>
<td>3/185</td>
</tr>
<tr>
<td>7/F/54</td>
<td>19</td>
<td>23</td>
<td>3/130</td>
</tr>
</tbody>
</table>

*Electrodes are numbered from 0 to 3 from the tip.
Image Acquisition

A venous cannula was inserted to administer tracer in the left arm. Positron emission tomography measurements were performed with a tomograph (EXACT-HR+; CTI-Siemens, Knoxville, Tenn) that allowed the 3-dimensional acquisition of 63 transaxial slices. Spatial resolution was 4.5 mm and 4.1 mm in the transaxial and axial directions, respectively. Regional cerebral blood flow images were acquired 10 minutes apart, for 80 seconds after the injection of 8 mCi of H15O.

DATA ANALYSIS

Image analysis was performed on a computer (SPARC station; Sun Microsystems Inc, Palo Alto, Calif) using statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, England). Images of each subject were realigned, normalized to Talairach space, and smoothed with a gaussian kernel of 12 mm full width at half maximum. Statistical parametric maps were generated using an analysis of covariance model after normalization for global cerebral blood flow changes.

Four effects were analyzed: (1) The movement effect compares the images obtained during hand movement with those acquired at rest and corresponds to the following computation: [(no stimulation during right-hand movement) + (low-frequency stimulation during right-hand movement) + (high-frequency stimulation during right-hand movement) − (no stimulation at rest)] (P<.01, Bonferroni corrected at P<.05 for multiple comparisons). The regions significantly activated by right-hand movements were then used as a mask for all following analyses. (2) The high-frequency stimulation effect compares conditions with the left STN high-frequency stimulation with the no-stimulation conditions, regardless of the movement condition: [(high-frequency stimulation at rest) + (high-frequency stimulation during right-hand movement) vs (no stimulation at rest)] (P<.01). (3) The low-frequency stimulation effect compares conditions with the left 10-Hz electrode stimulation with the no-stimulation condition: [(low-frequency stimulation at rest) + (low-frequency stimulation during right-hand movement) vs (no stimulation at rest)] (P<.01). (4) The interaction between stimulation and movement reveals the activations (P<.01) induced by the movement in each electrode condition, which corresponds to [(high-frequency stimulation during right-hand movement) − (high-frequency stimulation at rest)] − [(no stimulation during right-hand movement) − (no stimulation at rest)] and [(low-frequency stimulation during right-hand movement) − (low-frequency stimulation at rest)] − [(no stimulation during right-hand movement) − (no stimulation at rest)].

Finally, we analyzed with SPM99 the correlations between rCBF images obtained at rest in each electrode condition and the corresponding akinesia scores measured in the right hemibody. A mean rCBF image was calculated from the 2 images acquired at rest in each electrode condition and was correlated with the individual score obtained in the corresponding condition (P<.005, corrected for spatial extent >100 voxels). For each local maximum given by this analysis, we plotted the correlation between the local rCBF and the akinesia score using a software package (Statistica; Statsoft, Tulsa, Okla) with Bonferroni correction.

RESULTS

EFFECTS OF LEFT STN STIMULATION ON THE CONTRALATERAL PARKINSONIAN MOTOR SCORE

Compared with the no-frequency condition, high-frequency stimulation of the left STN improved parkinsonian symptoms in the right hemibody by 71% in patients not taking medication (Figure 1). Conversely, low-frequency stimulation did not improve motor symptoms (change =−1%) (Figure 1). During the PET study, no dyskinesia was observed, and the movement performance was significantly better during the high-frequency–stimulation condition (0.64±0.48) than during the low-frequency–stimulation (2.79±0.91) or no-stimulation (2.93±0.54) conditions (F2,6=73.2; P<.001), using the Scheffé post hoc test.

EFFECTS OF LEFT STN STIMULATION ON PET rCBF MEASUREMENTS

Movement Effect

Right-hand movements induced a significant activation (P<.001, Bonferroni corrected at P<.05) of motor and premotor cortical areas listed in Table 2.

Main Effect of the Left STN Stimulation on the Brain rCBF

Compared with the no-stimulation condition, the main effect of high-frequency stimulation (P<.01, corrected at P<.05) was to reduce the rCBF in several motor areas: the left primary sensorimotor cortex, the premotor cortex, the anterior cingulate cortex, the caudal supplementary motor area, and the right cerebellum (Table 3, Figure 2). In contrast, no significant rCBF change was observed during low-frequency stimulation when compared with no stimulation.

Interactions Between Movement and STN Stimulation

Left STN high-frequency stimulation during right-hand movements induced a statistically significant activation

Table 2. Regions Activated by Right-Hand Movements

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann Area</th>
<th>x, y, z*</th>
<th>z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sensorimotor cortex (L)</td>
<td>4</td>
<td>-40, -16, 42</td>
<td>6.3</td>
</tr>
<tr>
<td>Caudal supplementary motor area</td>
<td>2</td>
<td>2, -2, 52</td>
<td>6.6</td>
</tr>
<tr>
<td>Premotor cortex (L)</td>
<td>6</td>
<td>-52, 2, 18</td>
<td>4.5</td>
</tr>
<tr>
<td>Premotor cortex (R)</td>
<td>6</td>
<td>32, -6, 42</td>
<td>5.0</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>24</td>
<td>-14, 2, 34</td>
<td>3.8</td>
</tr>
<tr>
<td>Inferior parietal cortex (L)</td>
<td>40</td>
<td>-34, -36, 42</td>
<td>6.0</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>NA</td>
<td>12, -52, -12</td>
<td>6.7</td>
</tr>
<tr>
<td>Cerebellum (L)</td>
<td>NA</td>
<td>-40, -52, -26</td>
<td>5.2</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; NA, not applicable; R, right.

* x, y, z are Talairach coordinates.

Table 3. Areas Activated by Left STN Stimulation

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann Area</th>
<th>x, y, z*</th>
<th>z Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellum (L)</td>
<td>NA</td>
<td>-16, -58, -32</td>
<td>3.4</td>
</tr>
<tr>
<td>Caudal supplementary motor area</td>
<td>6</td>
<td>32, -6, 42</td>
<td>5.0</td>
</tr>
</tbody>
</table>
of the left primary sensorimotor cortex, the anterior cingulate cortex, and the right cerebellum (Figure 3). The plots of rCBF values measured at these coordinates revealed that these activations were related to a decreased rCBF at rest rather than an increase of rCBF during hand movements (Figure 3). Indeed, rCBF values during hand movement were not different between the high-frequency-stimulation and no-stimulation conditions. Low-frequency stimulation had no effect on movement-induced brain activation.

CORRELATION ANALYSIS

The severity of akinesia in the right hemibody was significantly correlated with rCBF values in the left primary sensorimotor cortex ($r=0.86; P<10^{-6}$ at local maximum) and the cerebellum ($r=0.87; P<10^{-6}$) (Figure 4).

In PD patients markedly improved by STN high-frequency stimulation, the main effect of the stimulation is to reduce the rCBF in several motor areas, this effect being maximal at rest. Moreover, the correlation analysis strongly suggests that the reduction of akinesia provided by STN high-frequency stimulation is related to this rCBF reduction in the motor cortex. These results support the idea that an abnormal hyperactivity in the cortical motor system at rest is a major feature of PD and that its reduction by STN high-frequency stimulation leads to motor improvement.

It has been considered that the selective reactivation of the midline premotor cortical areas (the supplementary motor area and the anterior cingulate cortex) is a landmark of the therapeutic action against akinesia. Several PET studies have evidenced selective activation of midline premotor cortical areas during hand movements in PD patients treated with apomorphine or levodopa. In addition, an activation of motor cortical areas including the supplementary motor area and the anterior cingulate was found with PET when studying the interaction between hand movement and STN high-frequency stimulation. Here, the combination of left STN high-frequency stimulation and right-hand movements selectively activated the left primary sensorimotor cortex, the right cerebellum, and the anterior cingulate cortex. Two mechanisms might explain these selective activations: an increase of rCBF during hand movement or

### Table 3. Regions Deactivated by Subthalamic Nucleus High-Frequency Stimulation

<table>
<thead>
<tr>
<th>Region</th>
<th>Brodmann Area</th>
<th>$x$, $y$, $z$</th>
<th>$z$ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary sensorimotor cortex (L)</td>
<td>4</td>
<td>-32, -18, 42</td>
<td>6.5</td>
</tr>
<tr>
<td>Premotor cortex (L)</td>
<td>6</td>
<td>-22, -12, 52</td>
<td>4.3</td>
</tr>
<tr>
<td>Anterior cingulate cortex</td>
<td>24</td>
<td>-6, -12, 42</td>
<td>3.9</td>
</tr>
<tr>
<td>Caudal supplementary motor area</td>
<td>6</td>
<td>-2, -22, 64</td>
<td>3.9</td>
</tr>
<tr>
<td>Cerebellum (R)</td>
<td>NA</td>
<td>10, -52, -12</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Abbreviations: L, left; NA, not applicable; R, right. $x$, $y$, $z$ are Talairach coordinates.

[Figure 2. Subthalamic nucleus high-frequency stimulation: regional cerebral blood flow decrease. A, Statistical parametric mapping (SPM99 Z-map) showing the decrease of regional cerebral blood flow induced by high-frequency stimulation applied through the left subthalamic nucleus. B, Regional cerebral blood flow decreases on the brain surface, showing the left primary sensorimotor cortex, the right cerebellum, the anterior cingulate, and the caudal supplementary motor area. L indicates left; R, right.]
a decrease of rCBF at rest in these regions. Careful analysis of the rCBF plots in these regions supports the second explanation (Figure 3). Thus, the selective activation of these regions is made possible by the reduction of rCBF at rest, which is the main effect of STN high-frequency stimulation, as in previous PET studies.5-7 This
suggested that such activations are made possible by the reduction of noisy activity at rest rather than enhanced activation during movement.

This rCBF reduction occurred in regions that are abnormally overactive in PD patients not taking medication. For example, Sabatini et al9 have shown that the primary sensorimotor cortex, the caudal supplementary motor area, the anterior cingulate, and the premotor cortex are overactive in PD patients not taking medication as compared with controls. In the same line, an abnormal cortical hyperactivity has been demonstrated at rest using transcranial magnetic stimulation in PD patients not taking medication. Moreover, the silent period after a voluntary movement is reduced in PD patients, suggesting a decreased activity of intracortical inhibitory systems.22 The consequence would be an abnormal increase of cortical neurons firing at rest in the motor cortex of parkinsonian subjects.23 Actually, the parkinsonian motor cortex–basal ganglia loop might be held abnormally in a 15-Hz to 30-Hz oscillatory state.11,12 This synchrony, which is present across many cells in both the STN and the motor cortex, could be responsible for akinesia in PD10-12 by leading to a suboptimal unfused pattern of muscle activation.24 The reduction of the basal ganglia 15-Hz to 30-Hz oscillations by dopaminergic drugs, neurosurgical lesioning, or STN high-frequency stimulation would therefore release the system from this hold state and overcome akinesia.8,21,25,26 Accordingly, the correlation found in this study between the severity of akinesia and the level of rCBF in the contralateral primary sensorimotor cortex suggests that the abnormal cortical overactivity in PD plays a direct role in the pathophysiology of akinesia and that its reduction by STN high-frequency stimulation is associated with akinesia improvement.

Left STN high-frequency stimulation also reduced the right cerebellar activity in the patients. The cerebellum is abnormally overactive in PD patients not taking medication.23 An abnormal cerebellar activity in PD patients might be attributed to tremor,28 rigidity,29 or akinesia.27 However, the tremor was absent in most of our patients. Moreover, the correlation analysis revealed that cerebellar rCBF was correlated with akinesia. Although cerebellar overactivity is reduced by STN high-frequency stimulation or levodopa treatment,27 the exact role of the cerebellum in the genesis of akinesia remains unclear.

The reduction of rCBF induced by STN high-frequency stimulation involved the lateral premotor cortex. Several studies revealed that PD patients have an abnormal overactivity of the lateral premotor cortex.9,30 This region would be recruited to compensate for the dysfunction of the mesial, internally activated premotor system. This might explain the improvement of motor function provided by external visual cues in PD patients. It is therefore possible that the improvement induced by STN high-frequency stimulation makes this compensatory premotor cortex activation unnecessary.31

In conclusion, we found that STN high-frequency stimulation allows the selective activation of several motor areas (primary sensorimotor cortex, anterior cingulate cortex, and cerebellum) during simple hand movements by reducing the abnormal overactivity in these regions, which is maximal at rest in PD patients. This overactivity is likely related to abnormal oscillatory activity in the motor cortex–basal ganglia loops in some of these regions, such as midline premotor areas and the primary sensorimotor cortex, or it might correspond to compensatory mechanisms in other areas, such as the premotor cortex. Therefore, reducing motor cortical overactivity appears to play a major role in the efficacy of STN high-frequency stimulation against PD symptoms.

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Figure 4. Correlation between akinesia and rest regional cerebral blood flow. A, Statistical parametric mapping (SPM99) “glass view” showing the regions where regional cerebral blood flow is positively correlated with the akinesia score in the right hemibody (P<.005). B, Plots obtained with a software package (Statistica) at the local maxima. Left primary sensorimotor cortex, r=0.86; P<.001. Cerebellum, r=0.87; P<.001. x, y, and z are Talairach coordinates.
REFERENCES